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## **Strengthening pharmacotherapy research for COVID-19-induced pulmonary fibrosis**

Liu YM *et al.* Research pharmacotherapy for COVID-19-induced PF

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**2**

### **Abstract**

The global spread of severe acute respiratory syndrome coronavirus 2 has resulted in a significant number of individuals developing pulmonary fibrosis (PF), an irreversible lung injury. This condition can manifest within a short interval following the onset of pneumonia symptoms, sometimes even within a few days. While lung transplantation is a potentially lifesaving procedure, its limited availability, high costs, intricate surgeries, and risk of immunological rejection present significant drawbacks. The optimal timing of medication administration for coronavirus 2019 (COVID-19)-induced PF remains controversial. Despite this, it is crucial to explore pharmacotherapy interventions, involving early and preventative treatment as well as pharmacotherapy options for advanced-stage PF. Additionally, studies have demonstrated disparities in anti-fibrotic treatment based on race and gender factors. Genetic mutations may also impact therapeutic efficacy. Enhancing research efforts on pharmacotherapy interventions, while considering relevant pharmacological factors and optimizing the timing and dosage of medication administration, will lead to enhanced, personalized, and fair treatment for individuals impacted by COVID-19-related PF. These measures are crucial in lessening the burden of the disease on healthcare systems and improving patients' quality of life.

**Key Words:** COVID-19; Pulmonary fibrosis; Pharmacotherapy intervention; Medication administration; Timing; Dosage

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**Core Tip:** Pulmonary fibrosis (PF) induced by coronavirus 2019 (COVID-19) represents a significant and serious complication of the disease. When PF advances to a critical stage, lung transplantation becomes the sole life-saving option. Our call is for an intensified focus on researching pharmacotherapy interventions for COVID-19-induced PF, aimed at identifying potential medication options.

## **INTRODUCTION**

Coronavirus 2019 (COVID-19) is a respiratory illness caused by the severe acute respiratory syndrome coronavirus 2. It has been observed that COVID-19 patients may develop pulmonary fibrosis (PF), a serious complication that affects their quality of life even after recovery<sup>[1]</sup>. PF is characterized by damage to the lung tissue, excessive scarring, and impaired lung function<sup>[2]</sup>. This often leads to respiratory failure and can be fatal<sup>[3]</sup>. It is important to explore pharmacotherapy interventions that can prevent or reduce fibrosis damage in COVID-19 patients<sup>[4]</sup>.

## **PATHOGENESIS OF COVID-19-INDUCED PF**

The pathogenesis of COVID-19-induced PF is complex and involves various molecular mechanisms. Transforming growth factor- $\beta$  and PI3K/AKT signaling pathways play important roles in the development of PF<sup>[5]</sup>. The activation of these pathways leads to fibroblast proliferation, migration, and conversion into myofibroblasts, resulting in excessive scarring<sup>[6]</sup>. Cytokine storm, characterized by an overactive immune response, also contributes to the activation, proliferation, and migration of fibroblasts<sup>[7]</sup>. Additionally, the EGFR pathway has been implicated in COVID-19-related PF<sup>[8]</sup>.

## **PHARMACOTHERAPY INTERVENTIONS**

### ***Medication commonly used in clinical treatment***

Pirfenidone and nintedanib are currently approved for the treatment of idiopathic PF and have shown efficacy in COVID-19-induced PF<sup>[4,9-11]</sup>. Pirfenidone inhibits fibroblast proliferation and extracellular matrix deposition, while nintedanib slows down the development of fibrosis<sup>[6,10]</sup>. Both medications have similar efficacy in reducing lung function decline<sup>[12,13]</sup>. However, pirfenidone may cause liver injury, and nintedanib is not recommended for patients with moderate or severe liver injury<sup>[14,15]</sup>.

### ***Medications less commonly used in clinical treatment***

N-acetylcysteine (NAC) and mesenchymal stem cell (MSC) therapy have shown potential as adjuvant treatments for COVID-19-induced PF. NAC replenishes glutathione levels and MSCs have anti-inflammatory and regenerative properties<sup>[16,17]</sup>. DPP-4 inhibitors and statins, commonly used for diabetes and cholesterol management, respectively, may also prevent fibrosis<sup>[7,18]</sup>. Anakinra, Xuanfei Baidu Decoction (a traditional Chinese medicine), nimotuzumab, and vitamin D supplementation have shown promising results in treating COVID-19-induced PF<sup>[19-22]</sup>.

#### *Potential medication therapies with limited evidence*

Several medications, such as natural polysaccharides, baicalin, the endocannabinoid system, dihydroartemisinin and (-)-Epigallocatechin-3-gallate, have shown anti-fibrotic effects in preclinical trials but lack clinical trial data<sup>[23-27]</sup>. Tocilizumab and baricitinib combination therapy has shown effectiveness but has controversial safety concerns<sup>[21,28]</sup>. PI3K inhibitors hold promise but require further exploration for safe use<sup>[29]</sup>.

### **PHARMACOLOGICAL CONSIDERATIONS ON ANTI-FIBROSIS TREATMENT FOR COVID-19-INDUCED PF**

When testing the effects of pharmacotherapy for COVID-19-induced PF, it is crucial to consider pharmacological factors. Studies have demonstrated that nintedanib exhibits comparable therapeutic effects across various ethnic groups, including Asian and White patients<sup>[15,30]</sup>. Additionally, the literature finding also confirms that the gender has no noticeable effect on nintedanib pharmacokinetics<sup>[15]</sup>. In terms of the utilization of anti-fibrotic treatment, Black patients are 40% less likely than their White counterparts to receive such treatment, and similarly, female patients are 59% less likely than their male counterparts<sup>[31]</sup>.

These findings offer valuable insights into potential disparities in the administration of anti-fibrotic treatment, highlighting the importance and potential significance of race and gender factors. Further research in this area holds great promise for exploring and understanding these disparities in greater detail, which can contribute to the

development of more personalized and equitable treatment approaches. Additionally, investigating the influence of race and gender on the effectiveness and safety profiles of anti-fibrotic therapies can provide a deeper understanding of their impact on different patient populations, ultimately leading to improved healthcare outcomes for all individuals.

In individuals with telomerase reverse transcriptase (TERT) mutations, there may be an increased risk of developing COVID-19-induced PF<sup>[32]</sup>. It has also been observed that TERT/TERC mutations are resistant to pirfenidone therapy<sup>[33]</sup>. Additionally, other genetic variants such as MUC5B, DPP9, and ATP11A have been associated with COVID-19-induced PF<sup>[34]</sup>. Exploring the role of genetics in this condition may <sup>4</sup> pave the way for the development of novel agents for targeted therapy and personalized treatment.

#### **TIMING AND DOSAGES OF MEDICATIONS PROPOSED FOR COVID-19-INDUCED PULMONARY FIBROSIS**

The optimal timing of medication administration for COVID-19-induced PF remains a topic of ongoing debate, with advocates for early and preventative approaches as well as those in favor of using anti-fibrotic drugs only when clear signs of PF with progressive exacerbations are present<sup>[7,10,35]</sup>. Each perspective is grounded in its own reasoning. Supporters of early intervention argue that COVID-19-induced PF might constitute an irreversible process, while those who are cautious about early treatment weigh the cost of anti-fibrosis treatment against the potential inevitability of COVID-19-induced PF. The nuances of these contrasting views underscore the complexity surrounding the optimal timing for administering anti-fibrotic drugs in the context of COVID-19-related complications. Further research on the timing of anti-fibrotic medication for PF caused by COVID-19 from both basic and clinical perspectives is necessary.

In order to achieve successful pharmacotherapy, proper dosages of promising drugs for anti-fibrosis treatment should be investigated. Table 1 summarizes the recommended dosages for some medications currently in use. Additionally, <sup>1</sup> the development of novel <sup>1</sup> drug delivery systems, such as inhalable systems including lipid-based nanocarriers,

nanovesicles, polymeric nanocarriers, protein nanocarriers, nanosuspensions, nanoparticles, gold nanoparticles, and hydrogel, could prove to be a promising area for the treatment of PF caused by COVID-19<sup>[36]</sup>.

## **CONCLUSION**

COVID-19-induced PF has emerged as a challenging problem with no known cure. Pharmacotherapy interventions aimed at delaying disease progression and improving quality of life are crucial. Pirfenidone and nintedanib are currently the mainstay of treatment, while other medications serve as potential adjuvant therapies. Rational use of DPP-4 inhibitors, statins, NAC, anakinra, vitamin D, and nimotuzumab may prevent or control the progression of COVID-19-induced PF. Traditional Chinese medicine and other experimental medications require further research and clinical trials to evaluate their efficacy and safety. Additional research is necessary to strengthen pharmacotherapy interventions aimed at managing COVID-19-induced PF, while taking into account relevant pharmacological factors and optimizing the timing and dosage of medication administration. Such efforts will lead to the development of enhanced, equitable, and personalized approaches to managing this condition.



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